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Antigen Presentation and T Lymphocyte Activation

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Lecture outline

- Dendritic cells and antigen presentation
- The role of the MHC
- T cell activation
- Costimulation, the B7:CD28 family

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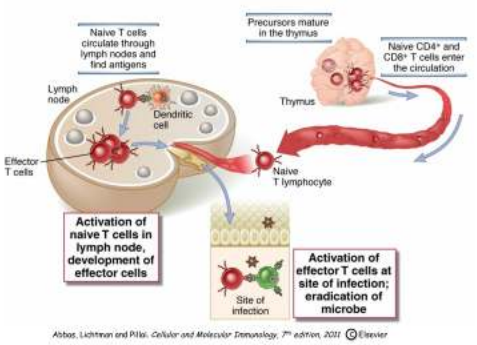
The life history of T lymphocytes



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The challenge for lymphocytes

- Very few lymphocytes in the body are specific for any one microbe (or antigen)
  - Specificity and diversity of antigen receptors: the immune system recognizes and distinguishes between 10^6 - 10^9 antigens; therefore, few lymphocytes with the same receptors

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The challenge for lymphocytes

- Very few lymphocytes in the body are specific for any one microbe (or antigen)
  - Specificity and diversity of antigen receptors: the immune system recognizes and distinguishes between 10^6 - 10^9 antigens
- Lymphocytes must be able to locate microbes that enter and reside anywhere in the body
  - Usual routes of entry are through epithelia, but infections may take hold anywhere

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The challenge for lymphocytes

- Very few lymphocytes in the body are specific for any one microbe (or antigen)
- Lymphocytes must be able to locate microbes that enter anywhere in the body
- Lymphocytes must respond to each microbe in ways that are able to eradicate that microbe; best exemplified by T cells
  - Extracellular microbes: antibodies; destruction in phagocytes (need helper T cells)
  - Intracellular microbes: killing of infected cells (need CTLs)
  - How do T cells distinguish antigens in different cellular locations?

Capture of antigens

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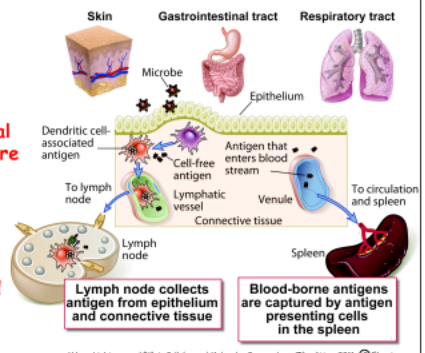
Sites of antigen entry

Sites of initial antigen capture

Sites of antigen collection and capture



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Capture and presentation of antigens by dendritic cells

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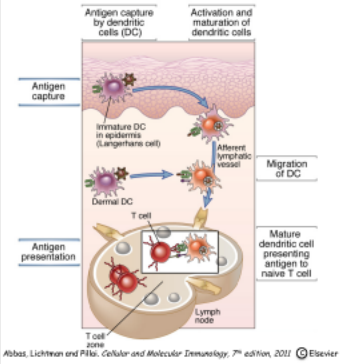

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Sites of microbe entry: *skin, GI tract, airways (organs with continuous epithelia, populated with dendritic cells). Less often -- colonized tissues, blood*

Sites of lymphocyte activation: *peripheral lymphoid organs (lymph nodes, spleen), mucosal and cutaneous lymphoid tissues*

Antigens and T cells come together in the same organs

Dendritic cell subsets

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- Classical: CD11c+, role in presentation of most antigens
- Plasmacytoid: source of type I IFN

- Immature: in tissues; role in presentation of self antigen and maintenance of tolerance
- Mature: activated by TLR and other signals; role in T cell activation

- Many other subsets described

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Why are dendritic cells the most efficient APCs for initiating immune responses?

- **Location:** at sites of microbe entry (epithelia), tissues
- **Receptors for capturing and reacting to microbes:** Toll-like receptors, other receptors
- **Migration to T cell zones of lymphoid organs**
  - Role of CCR7
  - Co-localize with naïve T cells
- **Maturation during migration:** Conversion from cells designed for antigen capture into cells for antigen presentation and T cell activation
- **Practical application:** dendritic cell-based vaccines for tumors

Take home messages

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What do T cells see?

- **All functions of T cells are mediated by interactions with other cells**
  - Helper T cells "help" B cells to make antibodies and "help" macrophages to destroy what they have eaten
  - Cytotoxic (killer) T lymphocytes kill infected cells
- **How does the immune system ensure that T cells see only antigens on other cells?**

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What do T cells see?

- **All functions of T cells are mediated by interactions with other cells**
  - Helper T cells "help" B cells to make antibodies and "help" macrophages to destroy what they have eaten
  - Cytotoxic (killer) T lymphocytes kill infected cells
- **To ensure cellular communications, T cells see antigens NOT in the circulation but only when displayed by molecules on the surface of other cells**
  - These molecules are HLA (generic name: MHC) and the cells displaying the antigen are APCs

Take home messages

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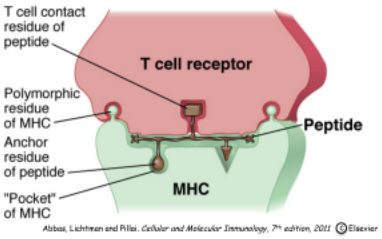
A model of T cell recognition of peptide displayed by an MHC molecule



Human MHC = HLA

Because MHC molecules are on cells and can display only peptides, T lymphocytes can recognize only cell-associated protein antigens

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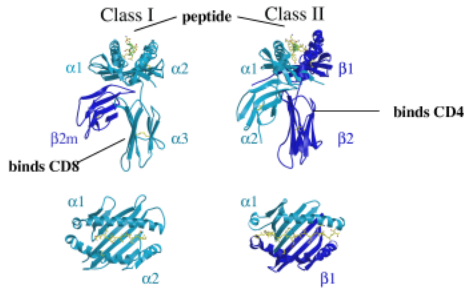
MHC Structures



All MHC molecules have a similar basic structure: the cleft at the N-terminal region binds peptide antigens and is recognized by T cell receptors and the membrane-proximal domain binds CD4 or CD8.

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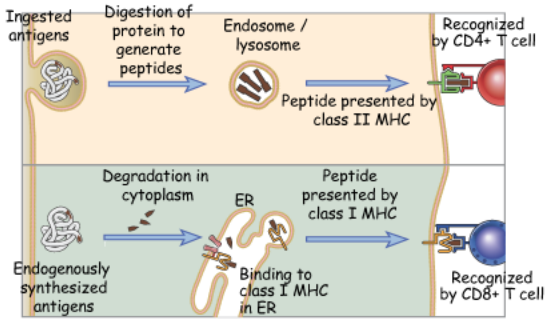
Pathways of antigen processing



Protein antigen in cytosol (cytoplasm) --> class I MHC -- CTLs
Protein antigen in vesicles --> class II MHC --> helper T cells

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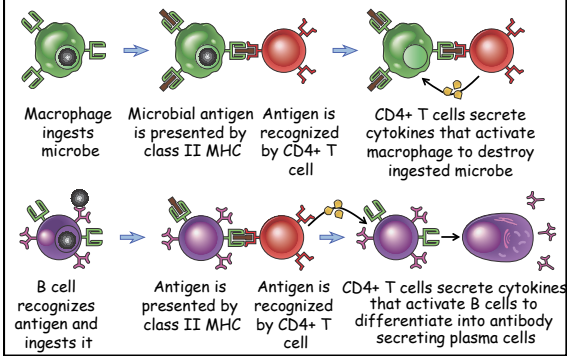
Functional importance of class II MHC-associated antigen presentation



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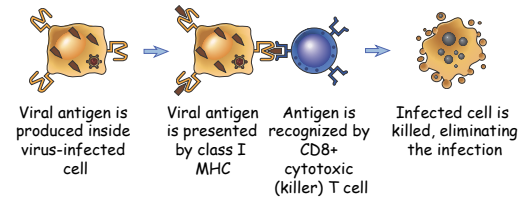
Functional importance of class I MHC-associated antigen presentation



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Functions of antigen-presenting cells

- **Capture antigens and take them to the "correct" place**
  - **Antigens are concentrated in peripheral lymphoid organs, through which naïve lymphocytes circulate**
- **Display antigens in a form that can be recognized by specific lymphocytes**
  - **For T cells: MHC-associated peptides (cytosolic peptides to class I, vesicular peptides to class II)**
  - **For B cells: native antigens**
- **Provide "second signals" for T cell activation**
  - **Critical for initiation of responses**

Take home messages

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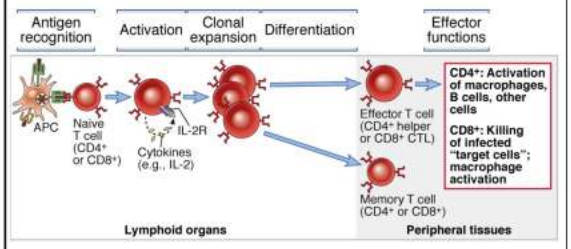
Steps in the activation of T lymphocytes



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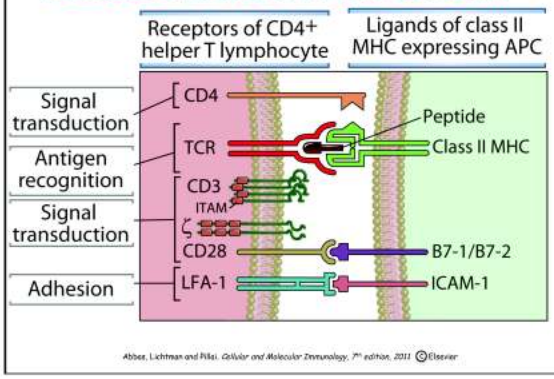
Molecules involved in T cell activation



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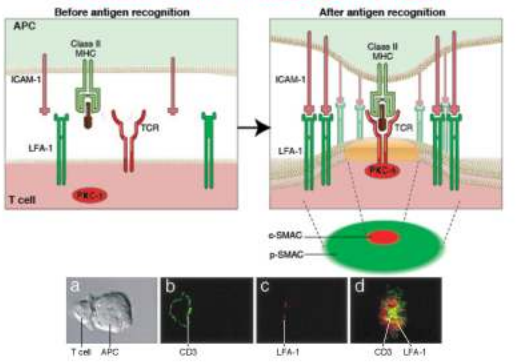
Formation of the immunological synapse



Regulated way of bringing together key signaling molecules

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Functions of the immune synapse

- Promote signaling
- Direct effector molecules to the relevant target: cytokines, CD40L, perforin, etc
- Terminate signaling: recruitment of phosphatases, ubiquitin ligases, inhibitory receptors (e.g. CTLA-4) to the site of the TCR complex

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Principal signaling pathways in T cell activation

- Membrane signal (TCR complex, other receptors) --> biochemical intermediates --> transcription factors
- Calcium -- calcineurin --> NFAT
- Ras/MAP-kinase --> AP-1
- PKC -- CARMA/BCL-10 --> NFκB
- PI3-kinase -- Akt --> NFκB
- Cytokines --> Jak-Stat

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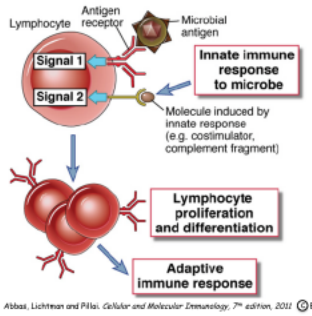
The two-signal requirement for lymphocyte activation



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Second signals for T cells: "costimulators" induced on APCs by microbial products, during early innate response

Second signals for B cells: products of complement activation recognized by B cell complement receptors

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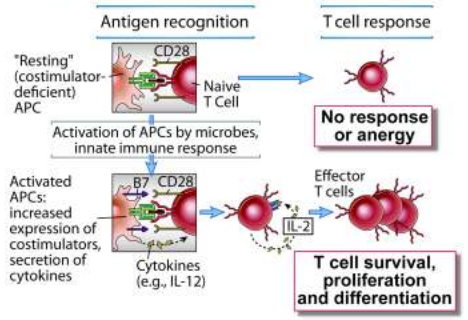
Role of costimulation in T cell activation



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Costimulation

- Required for initiating T cell responses (activation of naïve T cells)
- Ensures that T cells respond to microbes (the inducers of costimulators) and not to harmless antigens
  - Source of costimulation during responses to tumors, transplants?
- Targets for therapeutic blockade of T cell responses

Take home messages

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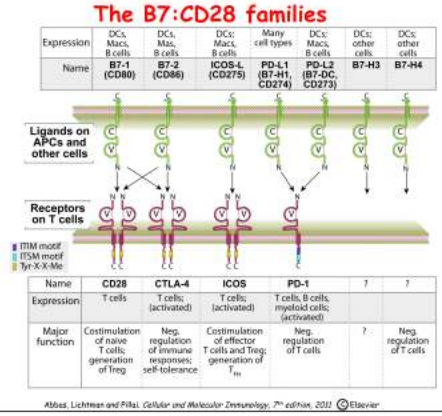
The B7:CD28 families



Expression	DCs, Macs, B cells	DCs, Mas, B cells	DCs; Macs, B cells	Many cell types	DCs; Macs, B cells	DCs; other cells	DCs; other cells
Name	B7-1 (CD80)	B7-2 (CD86)	ICOS-L (CD275)	PD-L1 (B7-H1, CD274)	PD-L2 (B7-DC, CD273)	B7-H3	B7-H4

Name	CD28	CTLA-4	ICOS	PD-1	?	?
Expression	T cells	T cells; (activated)	T cells; (activated)	T cells, B cells, myeloid cells; (activated)		
Major function	Costimulation of naive T cells; generation of Treg	Neg. regulation of immune responses; self-tolerance	Costimulation of effector T cells and Treg; generation of T_{FH}	Neg. regulation of T cells	?	Neg. regulation of T cells

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Major functions of selected B7-CD28 family members

Activation

- B7-CD28: initiation of immune responses
- ICOS-ICOS-L: T cell help in germinal center reactions (antibody responses)

Inhibition

- B7-CTLA-4: inhibits early T cell responses in lymphoid organs
- PD-1:PD-L1,2: inhibits effector T cell responses in peripheral tissues

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Complexities and unknowns of B7:CD28 costimulation

- Different T cell populations vary in their dependence on B7:CD28:
  - Naïve > activated > memory
  - CD4 > CD8
  - Regulatory T cells (controllers of immune responses) are also B7-dependent
- Redundancy of B7-1 and B7-2?
- Does B7 signal backwards into APCs?

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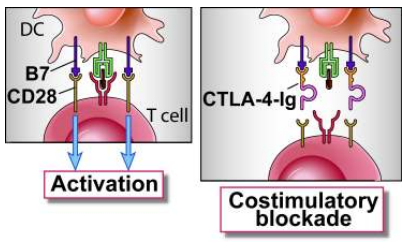
Therapeutics based on the B7:CD28 family
1. Costimulatory blockade



CTLA-4.Ig inhibits T cell activation in diseases caused by T cell responses-- rheumatoid arthritis, graft rejection, psoriasis

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Costimulatory blockade therapy

- B7-antagonist (CTLA-4.Ig, Abatacept) approved for RA, kidney allograft rejection (high-affinity version, Belatacept)
  - Risks:
    - Reducing responses against infections

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Costimulators other than B7:CD28

- Many proteins of the TNF-receptor family are expressed on T cells and implicated in T-cell activation and control
  - Functions often demonstrated in complex experimental systems or in vitro
  - Roles in disease (human or animal models) not definitely established
- Possible therapeutic targets?

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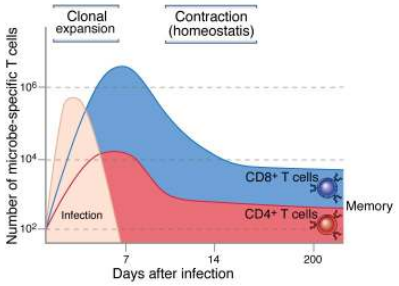
T cell expansion and contraction (decline)



Many aspects of T cell responses and functions are mediated by cytokines: initial activation -- IL-2; maintenance of memory cells -- IL-7; effector functions -- various

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Clonal expansion of T cells

- **Stimulated mainly by autocrine IL-2**
  - Antigen recognition → secretion of IL-2 and expression of high-affinity IL-2 receptors → preferential expansion of antigen-specific cells
- **CD8+ T cells may expand >50,000-fold within a week after an acute viral infection**
  - Up to 10% of all CD8+ T cells in the blood may be specific for a pathogen
  - Minimal expansion of "bystander" cells (not specific for the virus)
  - CD8+ cells expand much more than do CD4+ cells